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EDITED BY N. RASHEVSKY

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BULLETIN OF
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THE MATHEMATICAL BIOPHYSICS OF SOME MENTAL PHENOMENA: II. ANXIETIES AND ELATIONS

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A neural mechanism is discussed which explains certain states of anxieties, in which an individual is worried about things which may be possible, but are exceedingly improbable. Certain quantitative relations are derived. *Mutatis mutandis* similar considerations apply to some states of elations. An application to certain types of paranoia is discussed.

Any given situation which confronts an individual has, as a rule, a large number of possible consequences, of different degrees of probability, as well as different degrees of pleasantness. Thus, taking a walk may result in the mere sensation of walking, usually pleasant, and very probable. Or it may result in getting wet in a rain, which may be less probable and more unpleasant; or it may result in being injured by an automobile, which is rather improbable, but highly unpleasant; or it may result in finding a thousand-dollar bill, which is is also highly improbable, but exceedingly pleasant. Any given situation may be viewed as a complex stimulus pattern. Let us denote it by S.

If the same situation, or a set of similar situations, recurs frequently during the life time of an individual, then, since every time when it occurs, it is followed by one of the possible consequences, it becomes eventually associated through conditioning with *all* of those consequences. The strength of the association to a given consequence x_i will be the greater, the more frequently the sequence S,x_i has occurred in the past (Rashevsky, 1938a, chap. xxvi). But that frequency is proportional to the probability $P(x_i)$ of x_i occurring when S is present.

Through a mechanism discussed in a previous paper (Rashevsky, 1945a), when x_i becomes conditioned to or associated with S, then the experiencing of S makes us anticipate x_i in the future. The intensity of anticipation will be proportional to the strength of association. Thus any situation S would make us anticipate all, or almost all, possible consequences, if our experience with S has been long enough.

Let, however, all the centers for anticipation of different x_i's (Rashevsky, 1945a) be cross-inhibiting each other. Then only those that are most strongly excited, that is, the most probable ones, will remain excited, the remaining ones being inhibited. The intensity of excitation e_i of any x_i is given by

$$e_i = e_{0i} - b \sum_{k \neq i} e_{0k}, \tag{1}$$

where e_{0i} is the intensity as determined by the strength of association. For very large numbers of x_i, we may substitute an integral for the sum, considering x as a continuous variable:

$$e(x) = e_0(x) - b \int_0^\infty e_0(x)\,dx. \tag{2}$$

But, with α as a coefficient,

$$e_0(x) = \alpha P(x), \tag{3}$$

where $P(x)$ is the probability of x. Therefore

$$e(x) = \alpha P(x) - \alpha b \int_0^\infty P(x)\,dx, \tag{4}$$

or, since

$$\int_0^\infty P(x)\,dx = 1, \tag{5}$$

$$e(x) = \alpha [P(x) - b]. \tag{6}$$

If the inhibitory constant b is larger than the probability P_m of the most probable consequence x of S, then no consequences will be anticipated at all. This is a particular case of the general phenomenon of mutual inhibition of too many centers (Rashevsky, 1938, chap. xxii).

According to the theory of pleasantness and unpleasantness, developed before (Rashevsky, 1938a, 1940), the pleasantness of an experience is measured essentially by the intensity of excitation E of certain cortical regions, or perhaps even of the cortex as a whole. Since each x, or the anticipation of it, acts itself as a stimulus, therefore the experiencing of a given x or the anticipation of it, will result in a definite intensity of excitation $E(x)$ in the cortex.

In discussing problems of discrimination of intensities of peripheral stimuli, we pointed out (Rashevsky, 1938a, 1940) that since different reactions may be produced by different intensities of the same stimulus, those different intensities must involve different neu-

rons, or groups of neurons, even though the peripheral stimulus is applied always to the same afferent fibers or pathways (Rashevsky, 1945b). A mechanism was suggested which gives such an effect (Rashevsky, 1938b). It was further developed by A. S. Householder (1939, also Householder and Landahl, 1945) and successfully applied to a number of experimental data.

There is no sufficient reason to limit such considerations to intensities of peripheral excitation only. In fact, the generalization to central excitation is almost mandatory. We react quite differently to exhibit different degrees of pleasure or displeasure. Hence we must postulate a similar mechanism, which results in the excitation of different groups of neurons $N_{E(x)}$ for different values $E(x)$ of the central excitation.

If we now make the rather plausible assumption that all conditioned and associative connections are two-way connections so that if a stimulus s_1 is conditioned to a stimulus s_2, then s_2 is also conditioned to s_1, then we come to the conclusion that not only does the experiencing of x produce a central excitation $E(x)$ but, vice versa, if the central excitation has a given value $E(x)$ then, through the group of neurons $N_{E(x)}$ it will excite the center, whose functioning corresponds to the anticipation of x.

Let now the individual be confronted with the situation S and let at the same time the level of the central excitation be maintained at a given level $E(x')$ through some endogenous or exogenous influences. Then equation (3) will hold only for such values of x which are different from x'. For the latter we shall have

$$e_0(x') = \alpha P(x') + I, \tag{7}$$

where I denotes the additional excitation received by x' from the group of neurons $N_{E(x')}$. Instead of equation (2) we now have for $x \neq x'$

$$e(x) = e_0(x) - b\left[I + \int_0^\infty e_0(x)\,dx \right], \tag{8}$$

or instead of equation (6)

$$e(x) = \alpha [P(x) - b] - bI. \tag{9}$$

For $x = x'$ we have

$$e(x') = \alpha [P(x') - b] + I. \tag{10}$$

Whereas in the absence of the additional excitation I only the most probable x's are excited, now, even if $b < P_m$, the most probable $x = x_m$ may remain unexcited, while the one which is additionally excited by $N_{E(x')}$ will be excited. Or it may happen that while in

the neighborhood of $x = x_m$ the x's still remain excited, an $x = x'$, having the additional excitation I, will also be excited, even more strongly than x_m.

Let us arrange all x's in decreasing order of their pleasantness, so that $x = 0$ is the most pleasant. In the average life of an average individual most situations are of such a nature that their most probable consequences are neither too pleasant, nor too unpleasant. The extremely pleasant or extremely unpleasant consequences of S are as a rule improbable, as in the example given at the beginning of this paper. Hence $P(x)$ will have its maximum value P_n for some value of $x = x_m$, which is of average pleasantness. Let, for instance, $P(x)$ be a normal distribution

$$P(x) = \frac{1}{\sqrt{2\pi}\,\sigma} e^{-(x_m - x)^2/2\sigma^2}. \tag{11}$$

If the individual is confronted with S at a time when his central excitation level is in the neighborhood of $E(x_m)$, then all highly pleasant and highly unpleasant x's will be inhibited, and only the x's in the range between the two roots of the equation

$$a\,[P(x) - b] - bI = 0 \tag{12}$$

will be excited. The individual anticipates average, most probable events of average pleasantness. But if the situation S is confronted when the value $E(x)$ corresponds to $x' >> x_m$, then in the neighborhood of $x = x_m$ we shall have equation (9), but for x' we shall have expression (10). If $P(x)$ is given by equation (11), then

$$e(x') = a\left[\frac{1}{\sqrt{2\pi}\,\sigma} e^{(x_m - x')^2/2\sigma^2} - b\right] + I, \tag{13}$$

$$e(x_m) = a\left[\frac{1}{\sqrt{2\pi}\,\sigma} - b\right] - bI. \tag{14}$$

If

$$b < \frac{1}{\sqrt{2\pi}\,\sigma} < b\frac{I + a}{a}, \tag{15}$$

$$e(x') > 0, \tag{16}$$

then only x' will be excited. The individual anticipates such consequences of S which are unpleasant and unlikely. Because of equation (13), inequality (16) imposes a condition upon x'. Thus for given

α, b, I, σ, and x_m, the probability of x' may have to be above a certain value, in order that x' would be anticipated. If, however,

$$I > \alpha b, \tag{17}$$

then inequality (16) is always satisfied, but inequalities (15) may or may not be satisfied. If they are not, then besides x', x's in the neighborhood of x_m will also be anticipated.

Thus the lowering of the excitatory level $E(x)$ results in a shift of associations and anticipations of the consequences of a given situation towards such, which are unpleasant, and as a rule, highly improbable. We have an elementary mechanism of some anxiety neuroses when everything appears gloomy in the future and when an individual may worry over utterly unlikely possibilities. If at that moment a highly pleasant experience increases $E(x)$, and if this increase is not upset by some other influences (pathological conditions), the whole mood of the individual will change, and the future will appear "rosy".

Conversely, if an individual has an abnormally high level of $E(x)$, then, even in average circumstances, he will anticipate most pleasant, but unlikely events ($x << x_m$). The choice of the constants α, b, and I, together with the individuals normal level $E(x)$ determine for a given situation whether the individual is an optimist or a pessimist.

There may be a very great number of factors which can determine the average level of $E(x)$. In an individual who reacts rather emotionally to eating and likes very much good food, mere hunger or an upset stomach may lower $E(x)$ and produce temporarily a pessimistic attitude. On the other hand, a number of yet unknown or uncontrolled factors, like metabolism, endocrine activities, etc., may play an important role.

In a previous paper (Rashevsky, 1945a) we discussed possible mechanisms of some forms of paranoia. It may be pointed out that the mechanism discussed here can very well also give rise to paranoid conditions. In the present instance the paranoia may be due not to any defect of the mechanism of logical thinking, but to the *faulty choice of the premises*. A very large number of consequences *may* follow from a situation S. If, due to the above discussed mechanism, the individual chooses a very unlikely one, then with impeccable logic, he will arrive at deductions which will be in conflict with reality, and may lead the individual to social conflict. Thus, *purely logically*, there is the *possibility* that every other individual, with whom an individual A comes in contact, hates A and conspires against him. If A *accepts this* as the major premise, then if he sees that B is actually very

kind to him, the very impeccability of A's logic will force him to argue that B is kind to him in order to deceive him by his kindness. The roots of some paranoias may be not in the defect of logic, but in the defect of choosing the major premises. In real life this choice has in most cases to be made on probability bases. The mechanism discussed in this paper provides for the possibility of a forced choice of very improbable things.

Another interesting consequence of this theory is that an individual with low $E(x)$ will anticipate as a rule most unlikely things, and is apt to overlook the more likely ones. This may result in a number of unpleasant situations which might have been avoided, had the individual thought of more likely things. The unpleasant situation will lower $E(x)$ further, and thus the situation gets worse, until it may end in a psychosis.

In general, $P(x)$ is a function of time, $P(x,t)$. Instead of equation (3) we have

$$e_0(x,t) = \alpha \int_0^t P(x,t)\,dt = \alpha F(x,t). \tag{14}$$

The effect of the past experience of the individual is thus made explicit.

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CHAIN PROCESSES AND THEIR BIOPHYSICAL APPLICATIONS: PART II. THE EFFECT OF RECOVERY

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The biological effects of radiations are studied on the basis of a general probabilistic model of successive transformations (Markoff chains). The process of recovery is taken into account as a series of reverse transitions. The theory gives methods for calculating the probability of subjecting a microorganism to an observable change within an assigned time during a process of irradiation of a homogeneous aggregate of microorganisms. Two methods of calculation are given: one requires the solution of a secular equation, the other one consists of expansions in power series of the intensities of recovery.

1. The object of the paper. In Part I of this paper equations of some types of chain processes as they occur in biophysical applications, particularly in the study of biological effects of radiations, were given, and a general method of their solution was derived (Opatowski, 1945; this reference will be indicated as "Part I"). The purpose of the present Part II is to study these processes from a computational viewpoint, so that an evaluation of the theory on the basis of experimental material may be possible.

Because of the corpuscular character of radiations as well as of the biologic aggregates subject to experimentation, the phenomena in this field are of a probabilistic nature. Nevertheless, they have been presented in Part I in a deterministic manner as an approximation of the actual process. In the field with which we are mainly concerned the primary events consist of collisions of radiation quanta with single biological entities. Quite often we must bind our investigations to a certain cumulative effect of several such events. The probability of occurrence of an effective event in the sensitive volume is in general dependent on the events which already took place in the same volume, because in general each event produces some change of that volume. Processes of this type belong to the category known as Markoff chains. In our field the succession of single events is in general sufficiently rapid to enable us to apply the asymptotic theory of these processes and consequently to treat them formally in a deterministic manner, as has been done in Part I.

We assume that at least some of the events occurring in the sen-

sitive volume change the microorganism. These changes are interpreted as transitions of the organism to certain new states which are numbered $(0, 1, \cdots, i, \cdots n)$, 0 being the initial state and n a state under observation. Consider any two transitions of the type $(i - 1 \rightarrow i)$ and $(i + 1 \rightarrow i)$, where i has an assigned value. It is assumed that the probabilities for the occurrence of these transitions in any interval of time Δt are respectively $k_i \Delta t + o(\Delta t)$ and $g_i \Delta t + o(\Delta t)$, where k_i and g_i are independent of t and $o(\Delta t)$ are infinitesimals of higher order with respect to Δt. The probability of a transition within any interval of time Δt between two states which are not contiguous in the array $(0, 1, \cdots, n)$, is assumed to be also infinitesimal of higher order with respect to Δt. The transition $(i + 1 \rightarrow i)$ is interpreted as an effect of recovery, the transition $(i - 1 \rightarrow i)$ being in a more direct relation to the action of radiation. The function which is of interest in applying this probabilistic model to experimental results is the probability that the organism be at a time t in the state n if it was at the time $t = 0$ in the state 0. This probability function is the same $Y_n(t)$ to which a deterministic interpretation has been given in Part I.

The concept of chain processes for the study of biological effects of radiations has been suggested by F. Dessauer (1923) and developed by M. Blau and K. Altenburger (1923) in the particular case in which $g_i = 0$ and the k_i's are independent of i. The same case has been considered by J. A. Crowther (1926) and by many other authors (for a review of the subject see Koyenuma, 1943). In the absence of recovery, i. e., when $g_i = 0$, a general expression of $Y_n(t)$ has been known (Bateman, 1910; Opatowski, 1942). The case in which the k_i's are independent of i and the g_i's are either zero or equal to a constant g has been also solved recently (Opatowski, 1946). In the present paper methods for the calculation of $Y_n(t)$ are given in the general case when the g_i's and the k_i's depend on i. They will be applied in the next part of the paper to some more specific processes.

2. Calculation of $Y_n(t)$ *by solving a secular equation.* In Part I it has been found convenient to use besides $Y_n(t)$ also its Laplace transform, i.e.

$$y_n(s) = \int_0^\infty e^{-st} Y_n(t)\, dt = \mathfrak{L}\{Y_n(t); s\}. \tag{1}$$

A general expression of y_n is [Part I, equations (11) to (13)]:

$$y_n(s) = P_n / D(0, n), \tag{2}$$

where $P_n = \prod_{i=1}^{i=n} k_i$ and $D(0, n)$ is a determinant $||a_{r,c}||$ of order $n + 1$ defined by

$$a_{r,r} = s + k_{r+1} + g_{r-1}, \quad a_{r,r-1} = k_r, \quad a_{r,r+1} = g_r;$$
$$a_{r,c} = 0 \text{ for } |r - c| > 1; \quad 0 \leqq r, c \leqq n, \tag{3}$$

all quantities with a negative subscript being equal to zero by definition. If $s = -\bar{k}_i$ $(i = 1, 2, \cdots, n + 1)$ are the roots of the equation $D(0,n) = 0$ and if they are all different, then (Bateman, 1910)

$$Y_n(t) = P_n \sum_{i=1}^{i=n+1} \left[\prod_{j=1, j\neq i}^{j=n+1} (\bar{k}_j - \bar{k}_i) \right]^{-1} \exp(-\bar{k}_i t).$$

An expression of substantially the same type holds also when some of the roots are equal (Opatowski, 1942). However, if $g_i \neq 0$ and $n > 3$, the only known cases in which the roots of $D(0,n)$ may be calculated in "finite terms" are two: one solved by T. H. Rawles (1936, 1937) and M. Fréchet (1938) in which the intensities of transitions k_i, g_i are connected among themselves by a relation of a very special character, and the second in which $k_i = k$ and $g_i = g$ or $= 0$, k and g being two constants (Opatowski, 1946). In other cases the roots may be calculated by standard numerical methods. It is known that they are all real and negative with a possible exception of one which may be zero (Part I, Section 5). The following theorem by A. Stöhr (1943) gives a general method of locating these roots whatever are the values of the constants k_i and g_i: the interval formed by two consecutive roots of $D(0, n-1) = 0$ contains always one and only one root of $D(0, n) = 0$; if r_1 and r_2 are the smallest and the largest root of $D(0, n-1) = 0$, each of the intervals $(-\infty, r_1)$ $(r_2, +\infty)$ contains also one root of $D(0, n) = 0$. This theorem makes it possible to locate all the roots of $D(0, n) = 0$ starting, for instance, from $D(0, 3) = 0$, which can be solved algebraically. Another field which seems likely to yield a method of calculating the roots of at least some types of $D(0, n)$ is that of orthogonal polynomials, since the latter may be defined as proportional to the determinants of $D(0, n)$ (Szegö, 1939, p. 368). This method, which would involve an application of the known results concerning the zeros of orthogonal polynomials has not been investigated as yet, except in one case leading to Tchebychev polynomials (Opatowski, 1946).

Experimental results give usually some values of $Y_n(t)$ and no direct information as to the elements of the secular equation $D(0, n) = 0$. For this reason, in sections 3 and 4 an approximate expression

of $Y_n(t)$ will be derived whose use does not require the solution of that equation. It consists of expansions in power series of the intensities of recovery g_i.

3. Some preliminary formulae. We will need in the following sections the following formulae for the Laplace transform, for which the symbol of equation (1) will be used (see e.g. Doetsch, 1937, pp. 27, 62, 147-149, 155-164; Widder, 1941; Churchill, 1944, pp. 9-14, 21-39, 295):

$$\begin{aligned} \mathfrak{L}\left\{\int_0^t \phi(\tau)\psi(t-\tau)\,d\tau\,;\,s\right\} &= \mathfrak{L}\left\{\phi(t) * \psi(t)\,;\,s\right\} \\ &= \mathfrak{L}\left\{\phi(t)\,;\,s\right\}\ \mathfrak{L}\left\{\psi(t)\,;\,s\right\}, \end{aligned} \tag{4}$$

$$e^{-at} * F(t) = e^{-at}\int_0^t e^{at}F(t)\,dt\,, \tag{5}$$

$$\mathfrak{L}\{e^{-at}\,;\,s\} = 1/(s+a), \tag{6}$$

$$\mathfrak{L}\{(e^{-at}-e^{-bt})/(b-a)\,;\,s\} = \mathfrak{L}\{e^{-at} * e^{-bt}\,;\,s\} = 1/[(s+a)(s+b)], \tag{7}$$

$$\mathfrak{L}\{F^{(m)}(t)\,;\,s\} = s^m\,\mathfrak{L}\{F(t)\,;\,s\} - \sum_{i=0}^{i=m-1} s^{m-i-1}F^{(i)}(0)\,, \tag{8}$$

where $F^{(i)}(0) = [d^iF/dt^i]_{t=0}$ for $i \geqq 1$ and $F^{(0)}(0) = F(0)$,

$$\begin{aligned} \mathfrak{L}\{d(e^{-at} * e^{-bt})/dt\,;\,s\} &= \mathfrak{L}\{(ae^{-at} - be^{-bt})/(a-b)\,;\,s\} \\ &= s/[(s+a)(s+b)]\,. \end{aligned} \tag{9}$$

For our purpose it is sufficient to assume here that a and b are positive constants and that s is chosen in such a manner as to insure the validity of these formulae, which is always possible for the functions which we will have to consider. The function $F(t)$ must fulfill certain conditions which are, however, satisfied in our problems because we have to deal with entire functions. The symbol * is used for the so-called convolution, as explained by equation (4).

4. Calculation of $Y_n(t)$ *by expansion in series.* The type of expression which is obtained by expanding $Y_n(t)$ in power series of the intensities of recovery g_i may be seen in the following manner. The determinant $D(0, n)$ is a polynomial in the sums $(s+k_i)$ and may be written in the following form:

$$D(0, n) = \Pi_{n+1}[1 + \sum_m F_m(k_i, g_i)\ \Pi(m)/\Pi_{n+1}], \qquad (10)$$

where for brevity

$$\Pi_{n+1} = \prod_{i=1}^{i=n+1} (s + k_i), \qquad (11)$$

$F_m(k_i, g_i)$ is a polynomial of certain k_i's and g_i's and $\Pi(m)$ stands for a product of certain m terms $s + k_i$ with $m \leqq n$. If the term $[\cdots]$ in equation (10) is written as a polynomial in the g_i's and the ordinary rules of expansion of a reciprocal of a polynomial into a power series are applied, the following expression is obtained from equation (2):

$$\Pi_{n+1}\, y_n(s)/P_n = 1 - \sum_{j=1}^{\infty} \left[\Pi(p_j)/\Pi(q_j) \right] f_j(k_i) G_j(g_i), \qquad (12)$$

where $\Pi(p_j)$ and $\Pi(q_j)$ have a similar meaning as $\Pi(m)$, $p_j < q_j$, and $f_j(k_i)$ is a polynomial in k_i's, whereas $G_j(g_i)$ is a product of some g_i's or of their powers, the sum $\sum_j$ being extended for all such products for which $f_j(k_i) \neq 0$. Since $\Pi(p_j)$ is a polynomial in s of degree p_j, whose coefficients are polynomials in the k_i's, equation (12) may be written also in the form:

$$\Pi_{n+1}\, y_n(s)/P_n = 1 - \sum_{j=1}^{\infty} G_j(g_i) \sum_r f_{j,r}(k_i)\, [s^r/\Pi(q_j)], \qquad (13)$$

where the sum $\sum_r$ is taken for $r = 0, 1, \cdots p_j$ and $f_{j,r}(k_i)$ is a polynomial in the k_i's.

Now $Y_n(t)$ can be obtained from equations (1), (2), (13) and (4) to (9). We put for brevity

$$d_t{}^r = d^r/dt^r; \qquad e_i = \exp(-k_i t), \qquad (14)$$

$$\mathcal{E}_{n+1} = e_1 * e_2 * \cdots * e_n * e_{n+1}, \qquad (15)$$

and call $\mathcal{E}(q_j)$ the convolution of any q_j exponentials e_i, so that

$$\mathfrak{L}\{\mathcal{E}_{n+1}; s\} = 1/\Pi_{n+1}, \qquad \mathfrak{L}\{\mathcal{E}(q_j); s\} = 1/\Pi(q_j). \qquad (16)$$

Since the lowest term in the expansion of $\mathcal{E}(q_j)$ in power series of t is of degree $\geqq q_j - 1$ (see Opatowski, 1942), we have:

$$d_t{}^m\, \mathcal{E}(q_j) = 0 \text{ for } t = 0 \text{ if } m \leqq q_j - 2.$$

Therefore, by equation (8), since $r \leqq p_j \leqq q_j - 1$:

$$\mathfrak{L}\{d_t{}^r\, \mathcal{E}(q_j); s\} = s^r/\Pi(q_j).$$

Taking into account these relations, we obtain from equation (13)

$$Y_n(t)/P_n = 1 - \sum_{j=1}^{\infty} G_j(g_i) \sum_r f_{j,r}(k_i)\ \varepsilon_{n+1} * d_t^r\, \varepsilon(q_j)\,.$$

We proceed now to an explicit calculation of this expansion up to terms of second order in the intensities of recovery g_i. It may be seen from the expression (3) of the determinant $D(0, n)$ that a given g_i is contained only in the $(i+2)$-nd column which is

$$0, \cdots, 0, \quad g_i, \quad s + k_{i+2} + g_i, \quad k_{i+2}, \quad 0, \cdots, 0\,.$$

Consequently, the derivative of $D(0, n)$ with respect to that g_i is obtained by changing the above column into

$$0, \cdots, 0, \quad 1, \quad 1, \quad 0, \cdots, 0\,.$$

Since the second 1 is here an element of the main diagonal, it is clear that by drawing lines between the $(i+2)$-nd and $(i+3)$-rd rows and between the $(i+2)$-nd and $(i+3)$-rd columns, the determinant in question is split up into four square arrays, the elements of the left bottom array being all zero, those of the right bottom array forming the determinant $D(i+2, n)$ [cf. Part I, equation (13)] and those of the left top array forming a determinant which expanded according to the elements of the last column is

$$D(0, i) - k_{i+1} D(0, i-1)\,.$$

Consequently,

$$\partial D(0, n)/\partial g_i = [D(0, i) - k_{i+1} D(0, i-1)]\, D(i+2, n)\,. \qquad (17)$$

Actually, this relation holds only for $1 \leqq i \leqq n-2$. However, it is seen by a direct calculation that equation (17) holds also for $i = 0$ and $i = n-1$, if we put by definition

$$D(0, -1) = D(n+1, n) = 1\,.$$

Putting in $D(p, q)$ zeros for all the g_i's, all the elements of this determinant above the main diagonal become zero, so that

$$[D(p, q)]_0 = \prod_{i=p}^{i=q} (s + k_{i+1})\,, \qquad (18)$$

where the symbol $[\cdots]_0$ means that the calculation is carried out for all the g_i's put equal to zero. From equations (17), (18), and (11) we have now

$$[\partial D(0, n)/\partial g_i]_0 = s\, S(i+1, i+2)\, \Pi_{n+1}\,, \qquad (19)$$

where for brevity

$$S(i+1, i+2) = 1/[(s + k_{i+1})(s + k_{i+2})]\,. \qquad (20)$$

The latter symbol will be used in a general manner, viz.

$$S(p,q) = 1/\prod_{i=p}^{i=q} (s + k_i), \tag{21}$$

so that $\Pi_n = 1/S(1,n)$. Since a given g_i appears at most in one column of the determinant $D(p,q)$ [see Part I, equation (13)] its expansion will contain each g_i at most to the first power, so that the terms of higher order consist only of mixed products of the g_i's. These terms may be calculated in the following manner: the terms of the second order are

$$\sum_{i,j=0;j>i}^{n-1} \left[\partial^2 D(0,n)/\partial g_i\,\partial g_j\right]_0 g_i\,g_j, \tag{22}$$

and may be calculated by differentiating equation (17) with respect to g_j. It is clear from Part I, equation (13), that $D(p,q)$ contains only those g_j's for which $p-1 \leqq j \leqq q-1$. Consequently, on the right-hand side of equation (17) only $D(i+2, n)$ contains g_j's with $j \geqq i+1$. Therefore, we have for the general term of the sum (22):

$$\begin{aligned} &\partial^2 D(0,n)/\partial g_i\,\partial g_j \\ &= [D(0,i) - k_{i+1} D(0,i-1)]\,\partial D(i+2,n)/\partial g_j . \end{aligned} \tag{23}$$

But for $\partial D(i+2,n)/\partial g_j$ we may write an equation similar to expression (17):

$$\partial D(i+2,n)/\partial g_j = [D(i+2,j) - k_{j+1} D(i+2,j-1)]\,D(j+2,n), \tag{24}$$

with the condition that

$$D(i+2,i+1) = 1, \quad D(i+2,i) = 0, \tag{25}$$

so that for $j = i+1$ the term $[\cdots]$ in equation (24) equals 1 and for $j = i+2$ it equals $s + g_{i+1}$. Putting all the g_i's equal to zero we obtain from equations (23), (24), (25), (18), (11), (20), (21):

$$\left[\frac{\partial^2 D(0,n)}{\partial g_i\,\partial g_j}\right]_0 = \begin{cases} s\,S(i+1,i+3)\,\Pi_{n+1} & \text{for } j = i+1 \\ s^2\,S(i+1,i+2)\,S(j+1,j+2)\,\Pi_{n+1} & \text{for } j \geqq i+2 . \end{cases}$$

Consequently, the expansion of $D(0,n)$ up to terms of second order in the g_i's is

$$\begin{aligned} D(0,n)/\Pi_{n+1} = 1 + &\sum_{i,j=0;\,j\geqq i+2}^{n-1} s\,S(i+1,i+2)\,g_i + \\ &s^2\,S(i+1,i+2)\,S(j+1,j+2)\,g_i\,g_j + \sum_{i=0}^{i=n-2} s\,S(i+1,i+3)\,g_i\,g_{i+1} + \cdots . \end{aligned} \tag{26}$$

Higher order terms may be calculated in a similar manner. Expansion (26), and those which will now be derived from it, hold for any $n \geqq 2$. If $n = 1$, there is at most one g_i, viz., g_0, and the determinant (26) is a linear function of g_0.

Applying the known rule of division of power series, viz.,

$$1/(1 + \sum_{j \neq i} a_i x_i + a_{ij} x_i x_j + \cdots) =$$

$$1 + \sum_{j \neq i} - a_i x_i + a_i^2 x_i^2 + (2a_i a_j - a_{ij}) x_i x_j + \cdots,$$

we obtain from equations (2) and (26):

$$\begin{aligned} \Pi_{n+1} y_n(s)/P_n = 1 + \sum_{i,j=0, j \geqq i}^{n-1} - s\, S(i+1, i+2)\, g_i + \\ s^2\, S(i+1, i+2)\, S(j+1, j+2)\, g_i\, g_j - \\ - \sum_{i=0}^{i=n-2} k_{i+2}\, s\, S(i+1, i+2)\, S(i+2, i+3)\, g_i\, g_{i+1} + \cdots. \end{aligned} \tag{27}$$

The expression of $Y_n(t)$ may now be calculated from equations (27), (14) to (16), (20), (4) to (9), and the following formula:

$$\mathcal{E}_{m+1} = t^m\, e^{-kt}/m! \quad \text{if} \quad k_1 = k_2 = \cdots = k_{m+1} = k.$$

One obtains

$$\begin{aligned} Y_n(t)/P_n = \mathcal{E}_{n+1} + \mathcal{E}_{n+1} * \Big\{ \sum_{i,j=0; j \geqq i}^{n-1} - d_i (e_{i+1} * e_{i+2})\, g_i \\ + d_i^2 (e_{i+1} * e_{i+2} * e_{j+1} * e_{j+2})\, g_i\, g_j \\ - \sum_{i=0}^{i=n-2} k_{i+2}\, d_t [e_{i+1} * (te_{i+2}) * e_{i+3}]\, g_i\, g_{i+1} + \cdots \Big\}: \end{aligned} \tag{28}$$

The first term $\mathcal{E}_{n+1}$ of expansion (28) represents the effect of direct transitions alone, the remaining terms represent the effect of recovery. Each coefficient of this expansion is a sum of exponentials in t multiplied by a polynomial in t of degree $\geqq 0$. The calculation of $Y_n(t)$ according to expression (28) does not present any theoretical difficulty; it becomes, however, quite lengthly if the number of states is large. This inconvenience may be eliminated in some simple types of processes, as will be shown in the next part of the paper.

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A CONTRIBUTION TO THE MATHEMATICAL BIOPHYSICS OF CELL GROWTH AND SHAPES: II

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A theoretical study of the growing nerve cell filopodium is made using the assumptions of volume constancy, cylindrical shape, and substrate track of an earlier paper, but assuming additionally that a retarding force per unit area proportional to the rate of elongation is also acting. Equations of elongation for two different cases are derived.

In an earlier paper (Runge, 1945, hereinafter referred to as *loc. cit.*) a theory of the growth of nerve cell processes was presented. The theory covered two types of cell substrate relations corresponding to both isotropic and anistropic interfacial tension forces on the cell substrate interface.

In both of these cases the theory was developed both with and without frictional forces being taken into account.

The assumption made concerning the frictional force was that it was directed opposite to dz, where dz is an increment of length of the cell-process, and that its magnitude was given as $f_0 S_{cs}$, where f_0 is a constant and S_{cs} is the area of the cell substrate interface. Frictional forces acting on the cell medium interface were ignored in this discussion. The force $f_0 S_{cs}$ was assumed to act only when $dz/dt \neq 0$, and the essential feature of this discussion as far as frictional forces were concerned was that $f_0 S_{cs}$ was independent of dz/dt. However, since the cell-process is a plastic fluid, a truer picture of the adhesion between cell and substrate is obtained by stating that the adhesion force per square cm of *cs* (cell substrate) interface is given by a term $l_0\ dz/dt$, where l_0 is a constant of proportionality with dimensions $ML^{-2}T^{-1}$. Then the total friction force on the *cs* interface is given by the expression

$$l_0 S_{cs} \frac{dz}{dt}. \tag{1}$$

A similar argument involving the *cm* (cell medium) interface would give us a term

$$m_0 S_{cm} \frac{dz}{dt}, \tag{2}$$

for the total friction force on the *cm* interface. Making use of the equation of elongation of a viscous thread referred to as equation (15) in *loc. cit.* and the expressions (1) and (2), we obtain for our equation of elongation

$$\frac{1}{z}\frac{dz}{dt} = \frac{1}{3\eta A_0}\left\{F - (l_0 S_{cs} + m_0 S_{cm})\frac{dz}{dt}\right\} . \qquad (3)$$

In equation (3), η is the viscosity of cell-process, A_0 is the cross-sectional area of the cell-process, F is the resultant interfacial tension force parallel to the z-axis, and z is the length of the cell-process.

In the case of anistropic interfacial tension of the *cs* interface, this interface is approximately a flat rectangular strip, and the force F is given by the expression $-dE/dz$ in *loc. cit.* From equations (18) and (20) of *loc. cit.* we find

$$F = -6\,\eta(\pi - \beta)Q_0 r , \qquad (4)$$

while A_0, the cross-sectional area of the cell-process, is given as

$$A_0 = r^2(\pi - \beta). \qquad (5)$$

In equations (4) and (5), Q_0 is a constant and r is the radius of the cell-process and is related to z by the constant volume equation

$$r^2(\pi - \beta)z = V , \qquad (6)$$

where V is the constant volume of the cell-process and β is the contact angle of cell-process and substrate fiber.

In this case equation (1) of *loc. cit.* gives for S_{cs} and the longitudinal portion of S_{cm} the values

$$\left.\begin{aligned} S_{cs} &= 2rz\sin\beta \\ S_{cm} &= 2r(\pi - \beta)z \end{aligned}\right\} . \qquad (7)$$

Introducing equations (4), (5), (6), and (7) into equation (3), we obtain upon solving for dz/dt

$$\frac{dz}{dt} = \frac{Az^{3/2}}{B + Cz^{5/2}}, \qquad (8)$$

where

$$\left.\begin{aligned} A &= -6\,\eta(\pi - \beta)Q_0 > 0 \\ B &= 3\,\eta\sqrt{V(\pi - \beta)} > 0 \\ C &= 2[l_0 - m_0(\pi - \beta)] > 0 \end{aligned}\right\} . \qquad (9)$$

Inspection of equation (8) and inequalities (9) shows that $dz/dt > 0$ for $z > 0$; hence elongation once begun will continue indefinitely, unchecked by adhesion forces. Equation (8) shows that as $z \to \infty$, $dz/dt \to 0$.

Let us now consider the case of isotropic interfacial tension forces. The values of V, A_0, and S_{cs} are given by equations (43), (50), and (38) of *loc cit.*:

$$V = \pi(r^2 - a^2)z, \tag{10}$$

$$A_0 = \pi(r^2 - a^2), \tag{11}$$

$$S_{cs} = 2\pi az. \tag{12}$$

If we assume that m_0 is negligible, then introduction of equations (10), (11), and (12) into equation (3) gives

$$\frac{dz}{dt} = \frac{F}{\frac{3nV}{z^2} + 2\pi a l_0 z}. \tag{13}$$

If we also assume that γ_{cm} is negligible, then [Runge, *loc. cit.*, equation (49)] F will be constant and equation (13) may be written

$$\frac{dz}{dt} = \frac{Fz^2}{G + Hz^3}, \tag{14}$$

where

$$\left.\begin{aligned} G &= 3\eta V > 0 \\ H &= 2\pi a l_0 > 0 \\ F &= 2\pi a(\gamma_{ms} - \gamma_{cs}) \end{aligned}\right\}. \tag{15}$$

Inspection of equation (14) shows that $dz/dt = 0$ for $z = 0$ and $z = \infty$.

Inspection of equations (8) and (9) shows that $dz/dt > 0$ just in case $A > 0$, since B and C must exceed zero. This is equivalent to the condition $Q_0 < 0$, which is the necessary and sufficient condition for $dz/dt > 0$ in the anistropic case without friction, *loc. cit.*

From equations (14) and (15) we have that H and G must exceed zero, hence for $dz/dt > 0$, we must have $F > 0$, i.e., $\gamma_{ms} - \gamma_{cs} > 0$. This condition is not the same as the necessary and sufficient condition for $dz/dt > 0$, in the isotropic case without friction, as discussed in *loc. cit.* It should be recalled, however, that in the discussion referred to, the value of γ_{cm} was not treated as a negligible quantity. In neither case do we find a constant value for dz/dt. The functions of equations (8) and (14) will vary considerably with z for values of the coefficients which can be estimated from expected values of V, η, the γ's, a r, etc.

A necessary condition of F for a constant dz/dt can be obtained as follows. The equation of elongation for a viscous thread is

$$\frac{1}{z}\frac{dz}{dt}=\frac{F}{3\eta A}. \tag{16}$$

Since

$$Az=V, \tag{17}$$

we have after combining equations (16) and (17)

$$F=\frac{3\eta V}{z^2}\frac{dz}{dt}, \tag{18}$$

in other words, the force must vary inversely as the square of the length of the thread.

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A THEORY OF MEMBRANE PERMEABILITY: II. DIFFUSION IN THE PRESENCE OF WATER-FLOW

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The author's earlier treatment of diffusion through a membrane is extended to include the case in which there is a mass motion of water through the membrane. Water flows through the membrane in the direction from lower to higher concentrations of the solute. This water carries a part of the solute by convection. Thus in this general case there is a transport of solute through the membrane both in the direction from higher to lower concentration, and in the opposite direction. If the latter effect prevails, the net result is a flow of solute from lower to higher concentrations. Mathematically this corresponds to negative values of the permeability. The effect of hydrostatic pressure is considered also.

In a previous study (Bloch, 1944) the author developed some general expressions for the permeability of a membrane, regarded as a potential well or barrier. In the present paper the effect of flow of water through the membrane will be discussed. Water flows from the side of the membrane on which the concentration of the solute is smaller, to that on which it is greater. This flow of water is thus opposed to the flow of the solute. As a result, there is a tendency for the molecules of the solute to be dragged by that water flow in a direction opposite to that of the normal diffusion flow. Under certain conditions this convective effect of the water flow may exceed the effect of diffusion transport through the membrane, and the solute then will flow from lower to higher concentrations. Formally this situation is described by a negative value of the permeability of the membrane to the solute.

Although the discussions in this paper are still on a rather abstract level, even in this preliminary form they may give a clue to the well known phenomena of accumulation of electrolytes in cells, with transport *towards higher concentrations.*

The notation used in the author's earlier paper on membrane permeability (Bloch, 1944) will, with a few slight changes, be kept here. In addition let

I = flow of water, in gm/cm² sec, in the $+ x$ direction,

h = permeability of the membrane to flow of the solute,

J = flow of the solute, in gm/cm² sec, in the + x direction,

$W(x)$ = potential energy of a solute molecule as a result of the flow of water,

P_0, P_1 = hydrostatic pressures on the two sides of the membrane.

The permeability for water is usually defined as the flow of water per unit area per unit difference of osmotic pressures on the sides of the membrane (Rashevsky, 1938, p. 101; Oppenheimer and Pincussen, 1933). Since the osmotic pressure is proportional to the concentration, the permeability H for water is here defined as the flow per unit area per unit difference of the concentrations of the solute on the two sides of the membrane.

The effect of water-flow on the diffusion of a solute through a membrane is equivalent to the superposition upon the membrane potential function $V(x)$ of a function $W(x)$, the potential energy per gram of the solute as a result of water-flow. If it is assumed that a flow I of water in the absence of a solute concentration gradient produces a flow of solute

$$J = cI\,,* \tag{1}$$

then $W'(x)$ may be obtained for this case:

$$\frac{cW'}{kT} = -\frac{cI}{D}. \tag{2}$$

If W', as obtained from equation (2), is substituted in the general equation for $c(x)$ (Bloch, 1944), the result is

$$c' + \frac{cV'}{kT} - \frac{cI}{D} = -\frac{J}{D}. \tag{3}$$

The solution of equation (3) is

$$c = e^{-\int (V'/kT - I/D)\,dx} \left[a - J \int_{-B_1}^{x} \frac{e^{\int (V'/kT - I/D)\,dx}}{D}\,dx \right]. \tag{4}$$

As before,

$$\int \frac{V'dx}{kT} = -\frac{3}{2} \log \left(T_0 - \frac{2}{3k} V \right), \tag{5}$$

* This is inaccurate because the membrane will resist the entrainment of solute by water.

whence

$$c_0 = \left(T_0 - \frac{2}{3k} V \right)^{3/2} \left\{ \exp \left[I \int (dx/D) \right] \right\}$$

$$\times \left[a - J \int_{-B_1}^{x} \frac{[T_0 - (2/3k) V]^{-3/2} \exp[-I \int (dx/D)]}{D} dx \right]. \tag{6}$$

Now

$$c_0 = T_0^{3/2} a \exp \left[I \int_{-B_1} (dx/D) \right]. \tag{7}$$

If $\int_{-B_1}$ and $\int_{B_2}$ denote integrals evaluated at $x = -B_1$ and at $x = B_2$, respectively, then

$$c = \left(T_0 - \frac{2}{3k} V \right)^{3/2} \left\{ \exp \left[I \int (dx/D) \right] \right\}$$

$$\cdot \left[\frac{c_0}{T_0^{3/2} \exp \left[I \int_{-B_1} (dx/D) \right]} \right. \tag{8}$$

$$\left. - J \int_{-B_1}^{x} \frac{[T_0 - (2/3k) V]^{-3/2} \exp [-I \int (dx/D)]}{D} dx \right].$$

Also

$$c_1 = T_0^{3/2} \left[\frac{c_0}{T_0^{3/2} \exp I \int_{-B_1} (dx/D)} \right.$$

$$\left. - J \int_{-B_1}^{B_2} \frac{[T_0 - (2/3k) V]^{-3/2} \exp [-I \int (dx/D)]}{D} dx \right] \cdot \tag{9}$$

$$\exp \left[I \int_{B_2} (dx/D) \right],$$

or

$$c_1 = c_0 \exp \left[I \int_{-B_1}^{B_2} (dx/D) \right]$$

$$- J T_0^{3/2} \int_{-B_1}^{B_2} \frac{[T_0 - (2/3k) V]^{3/2} \exp \left[I \int_{x}^{B_2} (dx/D) \right]}{D} dx. \tag{10}$$

It is sufficient here to treat the special case

$$\begin{aligned} &V = 0 \text{ for } x < -b \text{ and for } x > b; \\ &V = V_0 \text{ for } -b \leqq x \leqq b; \\ &b = B_1 = B_2. \end{aligned} \tag{11}$$

Let

$$D(x) \equiv D_0 \text{ for } -b \leqq x \leqq b;$$
$$\gamma \equiv \exp\left[I - \int_{-b}^{+b} (dx/D)\right]. \tag{12}$$

Now

$$\gamma \equiv e^{2bI/D_0}, \tag{13}$$

and

$$\exp\left[I \int_x^b (dx/D)\right] = \exp\left[I/D_0(b-x)\right] \quad \text{for } -b \leqq x \leqq b. \tag{14}$$

Hence

$$\begin{aligned} c_1 &= \gamma c_0 - J \int_{-b}^{b} \frac{[1-(2V_0/3kT_0)]^{-3/2}}{D_0} e^{I/D_0(b-x)}\, dx \\ &= \gamma c_0 + \frac{J}{I}\left(1 - \frac{2V_0}{3kT_0}\right)^{-3/2}(1-\gamma). \end{aligned} \tag{15}$$

The quantity h is defined as follows:

$$h \equiv \frac{J}{c_0 - c_1}. \tag{16}$$

Therefore,

$$\begin{aligned} h &= \frac{J}{\gamma c_0 - c_1} \frac{\gamma c_0 - c_1}{c_0 - c_1} \\ &= \frac{I}{\gamma - 1}\left(1 - \frac{2V_0}{3kT_0}\right)^{3/2} \frac{\gamma c_0 - c_1}{c_0 - c_1}. \end{aligned} \tag{17}$$

If in the absence of a difference of concentrations ($c_0 = c_1$), there is a difference of hydrostatic pressures on the two sides of the membrane, then the flow is proportional to that difference; hence, in general,

$$\begin{aligned} I &= H(c_1 - c_0) + K(P_0 - P_1) \\ &\equiv \frac{D_0}{2b}\left[(v-u) + (y-z)\right], \end{aligned} \tag{18}$$

where

$$u \equiv \frac{2bH}{D_0} c_0, \qquad y \equiv \frac{2bK}{D_0} P_0,$$
$$v \equiv \frac{2bH}{D_0} c_1, \qquad z \equiv \frac{2bK}{D_0} P_1. \tag{19}$$

The constants H and K are not independent. Approximately $H = RTK/M$, where R is the gas constant and M the molecular weight. Thus

$$h = \frac{1}{1 - e^{2b/D_0[H(c_1-c_0)+K(P_0-P_1)]}} \left(H - \frac{K(P_0 - P_1)}{c_0 - c_1} \right) \left(1 - \frac{2V_0}{3kT_0} \right)^{3/2} \left(c_0 e^{2b/D_0[H(c_1-c_0)+K(P_0-P_1)]} - c_1 \right), \tag{20}$$

or

$$h = \left(H - \frac{K(P_0 - P_1)}{c_0 - c_1} \right) \left(1 - \frac{2V_0}{3kT_0} \right)^{3/2} \times \frac{c_0 e^{2b/D_0 (KP_0 - Hc_0)} - c_1 e^{2b/D_0 (KP_1 - Hc_1)}}{e^{2b/D_0 (KP_1 - Hc_1)} - e^{2b/D_0 (KP_0 - Hc_0)}}, \tag{21}$$

or, by equations (19),

$$h = \frac{D_0}{2b} \left(1 - \frac{y - z}{u - v} \right) \left(1 - \frac{2V_0}{3kT_0} \right)^{3/2} \frac{ue^{y-u} - ve^{z-v}}{e^{z-v} - e^{y-u}}. \tag{22}$$

In this paper discussion is confined to the special case in which $y = z$, or there is no difference between the hydrostatic pressures on the two sides of the membrane, discussion of the more general case in which $y \neq z$ being left to another paper. If $y = z$,

$$h = \frac{D_0}{2b} \left(1 - \frac{2V}{3kT_0} \right)^{3/2} \frac{ue^{-u} - ve^{-v}}{e^{-v} - e^{-u}}. \tag{23}$$

In view of the fact that permeability can be negative only when water flow is sufficient to make the solute flow from regions of lower to regions of higher concentration, it can be seen from equation (18) that h is most likely to be negative when H is large, while equation (1) shows that, *ceteris paribus*, negative values of h should accom-

pany large values of c_0 and c_1. Thus, the definitions of u and v being given by equation (19), negative permeabilities might be expected to result from large values of these quantities, as is indicated by Figure 1.

Here the line $h = 0$ is the curve $ue^{-u} = ve^{-v}$ in the uv plane; in the region below and to the left of this line,

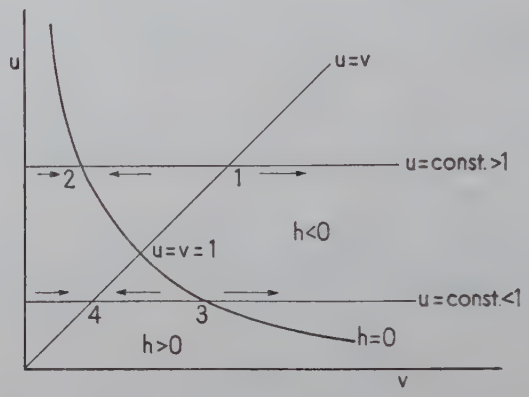

FIGURE 1

$$\frac{ue^{-u} - ve^{-v}}{e^{-v} - e^{-u}} > 0,$$

or

$$h > 0, \tag{24}$$

while above and to the right of this line

$$h < 0. \tag{25}$$

In biological systems a relation often exists between c_0 and c_1, and hence between u and v. Such relations may be given, for instance, by the diffusion equation. In the case of a single cell in an infinite medium with constant concentration c_0 outside the cell, then

$$u = \text{const.}; \tag{26}$$

In the case of an isolated non-metabolizing system of two cells, or other regions, of constant volume with a membrane between them, the equation is

$$\varepsilon u + \eta v = \mu, \tag{27}$$

where ε and η are proportional to the volumes of the two regions, and μ is proportional to the total amount of solute present in the system.

The state of a system is represented by a point on the graph, in the uv plane, of its equation of state. As time passes, this point moves along the locus of the equation of state toward or away from the line $u = v$ according as h is positive or negative.

Figure 1 illustrates some possible behaviors of the single cell in an infinite medium, whose equation of state is equation (26).

If $u > 1$, the equation of state is represented by the upper horizontal line in the figure. If now the initial state of the system is represented by a point to the right of point 1, this point moves farther and farther to the right as time passes, h being negative. This means that water flowing into the cell carries solute with it more rapidly than the solute can diffuse in the other direction. If, on the other hand, the initial state of the system corresponds to a point between point 1 and point 2, the representative point moves to the left until it reaches point 2; if the representative point starts to the left of point 2, it moves to the right to point 2. Thus point 2 represents a stable configuration of the system: the representative point of the system returns to it after a small displacement from it in either direction. This means that if, initially, $u > 1$ and $v < u$ (i.e., the concentration of solute in the cell is less than that outside), v has a stable value less than the value of u, at which value it remains as long as water is able to flow from the cell fast enough to maintain the concentration difference across the cell membrane.

If the cell is in a medium for which $u < 1$, the state of the system is represented by a point on the lower horizontal line in Figure

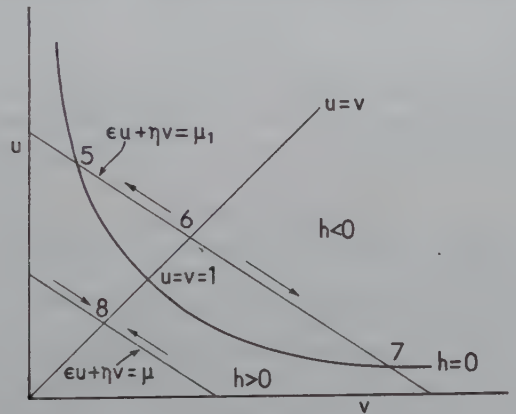

FIGURE 2

1. In this case the representative point moves to the right without limit if it has started to the right of point 3; if it has started to left of point 3, it reaches the stable point 4 and stays there. In this

latter case, the stable state is one in which there is no flow of water, the concentrations of the solute being equal inside and outside the cell.

The case of two coupled cells, whose equation of state is equation (27), is illustrated in Figure 2.

The upper of the two downward sloping straight lines represents the equation of state for the case in which this line cuts the curve $h = 0$ (i.e., the case in which $\mu > \varepsilon + \eta$). Reasoning similar to that applied in the preceding cases shows that if the representative point starts from the right of point 6 on the line $\varepsilon u + \eta v = \mu_1$, it goes to the stable point 7, while if it starts from the left of point 6, it goes to the stable point 5. Flow of water from one region to the other is needed to maintain the system in a steady state corresponding to either point 5 or point 7.

In the case illustrated by the lower of the two downward sloping straight lines in Figure 2 (the case in which $\mu \leqq \varepsilon + \eta$), there is only one stable state, that represented by point 8; maintenance of this state does not require water flow.

It is interesting that, at least in the two cases considered, a stable state can exist in which the concentrations of solute on opposite sides of a permeable membrane are different. However, in both these cases the concentration differential of the solute is maintained only as long as water is able to flow fast enough. Thus the "steady" states in question can be really steady for long times only if there is rapid water metabolism, and even in this case the other metabolites are probably flowing in great enough quantities to influence the concentration of any other solute about as much as does the flow of water. Thus it appears that the type of treatment given here is somewhat unrealistic for any system of two regions, one of which is closed. The treatment of the case involving two non-closed regions (e.g., the case of diffusion from capillaries, as in the kidney) is complicated by the fact that v cannot be expressed as a unique function of u.

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THE NEURAL MECHANISM OF LOGICAL THINKING

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A theory of such neural circuits is developed which provide for formal logical thinking. As a by-product of this study, a neural mechanism is indicated which provides for the conception of ordinal numbers. A quantitative theory of the probability of erroneous reasoning and of the speed of reasoning in its relations to other psychological phenomena is suggested.

In a previous paper (Rashevsky, 1945a) on this subject we suggested that neuron circuits, which will explain formal logical thinking, may be constructed by the use of the symbolic logic method of W. S. McCulloch and W. Pitts (1943). To use this method we need, however, some assumptions about what constitutes the neurophysiological counterpart of such statements as "all *A*'s are *B*'s" or "some *A*'s are *B*'s", etc.

I

One of the simplest assumptions is to consider a statement like "all *A*'s are *B*'s" as a stimulus pattern consisting of the sequence of the stimulus *A* , a stimulus corresponding to the notion "all . . . . are", and of the stimulus *B* . In ordinary language the stimulus *"A"* is actually preceded by "All" and followed by "are". This complicates the situation somewhat, but does not change it in principle. If we use symbolical notations, we may write *"AaB"*, in which case we do have a sequence of of three stimuli.

Therefore, without any loss of generality, we may consider that the statements "All *A*'s are *B*'s", "Some *A*'s are *B*'s", "No *A*'s are *B*'s", and "Some *A*'s are not *B*'s" are temporal sequences of stimuli *"AaB"*, *"AiB"*, *"AeB"*, and *"AoB"*. Then we may say that a logical inference of the mode "barbara" is made if the presentation of the sequence *"AaBCaA"* is automatically followed by *"CaB"*. Similarly, an inference of the mode "darii" is made when the sequence *"AaBCiA"* is followed by *"CiB"*.

Let the perception of *"A"* correspond to the excitation of the neuron N_A , the notation *"a"* ("all-are"), to the excitation of neuron

N_a, etc. Then, using the same notations as in a previous paper (Rashevsky, 1945b), a network which is described by

$$\begin{aligned} N_C(t) &\equiv N_A(t-6) \cdot N_a(t-5) \cdot N_B(t-4) \\ &\quad \cdot N_C(t-3) \cdot N_i(t-2) \cdot N_A(t-1)\,; \\ N_i(t+1) &\equiv N_A(t-6) \cdot N_a(t-5) \cdot N_B(t-4) \\ &\quad \cdot N_C(t-3) \cdot N_i(t-2) \cdot N_A(t-1) \cdot N_C(t)\,; \\ N_B(t+2) &\equiv N_A(t-6) \cdot N_a(t-5) \cdot N_B(t-4) \\ &\quad \cdot N_C(t-3) \cdot N_i(t-2) \cdot N_A(t-1) \cdot N_C(t) \cdot \\ &\quad N_i(t+1), \end{aligned} \tag{1}$$

may be said to be able to "reason" in the mode of "darii". There is no difficulty in constructing networks for different modes of the Aristotelian logic, by using the method of W. S. McCulloch and W. Pitts.

Such a procedure, however, has several weak points, of which we first discuss one. The circuit, represented by equations (1), is timed in such a way that the stimuli *A*, *a*, *B*, *C*, *i*, *A*, etc., follow each other at intervals of one synaptic delay, that is, about 0.5 ms. By the intercalation of a proper number of internuncials, it is easy, however, to make this interval as long as desired. It is also possible to make the intervals between different stimuli of the sequence not equal. But in all cases *those intervals are fixed* in their magnitude. This is neurophysiologically and psychologically, to say the least, very unplausible. What is needed, for instance, in the case of the mode "darii" is that the sequence *"CiB"* shall follow the sequence *"AaBCiA"*, regardless of the intervals between the individual items of the sequence.

To construct such a circuit we must first study a simpler circuit, namely, one described by

$$\begin{aligned} N_3(t) \equiv\ & [(Ex)N_1(t-x)] \cdot [(Ey)N_2(t-y)] \\ & \cdot [x > y + m] \cdot [y \geqslant n], \end{aligned} \tag{2}$$

where m and n are positive integers.

As has been shown previously (Rashevsky, 1945b), such a circuit requires the introduction of closed circles of neurons. The circuit which realizes expression (2) for $m = 0$, $n = 3$ is represented in Figure 1. The thresholds of all the neurons, measured in terms of the minimum number of terminal bulbs which must be excited within the period of latent addition, are assumed to be equal to 2.

In any actual situation, the intervals between any stimuli involved in logical thinking are of the order of at least several hundred σ's and usually even much larger. This means a very large m. To simplify notations, we shall in the following write simply $x >> y$.

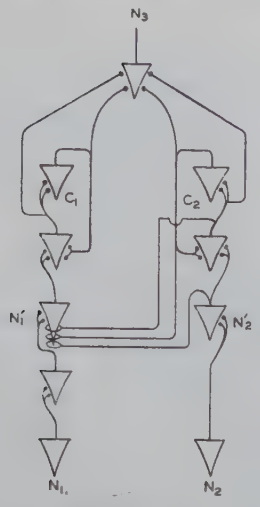

FIGURE 1

Because of the inhibitory fibers going from C_2 to N_1', C_1 cannot become excited if N_2 fires before N_1. If N_1 fires before N_2, then both C_1 and C_2 become permanently excited, and N_3 receives at regular intervals σ two impulses simultaneously.

We introduce the following abbreviation, denoting by x, y, z, and u positive integers,

$$\begin{aligned} N_i : N_k : N_p : \cdots N_r \equiv\ & [(Ex)N_i(t-x)] \cdot [(Ey)N_k(t-y)] \\ & \cdot [(Ez)N_p(t-z)] \cdot \ldots [(Eu)N_r(t-u)] \\ & \cdot [x >> y >> z >> \cdots >> u > n] . \end{aligned} \tag{3}$$

From such circuits as shown in Figure 1, we may now construct a circuit which realizes the following expressions, in which p and q again denote positive integers,

$$\begin{aligned} N_C(t) &\equiv N_A : N_a : N_B : N_C : N_i : N_A ; \\ N_i(t+p) &\equiv (N_A : N_a : N_B : N_C : N_i : N_A) \cdot N_C(t) ; \\ N_B(t+p+q) &\equiv (N_A : N_a : N_B : N_C : N_i : N_A) \cdot N_C(t) \cdot N_i(t+p) . \end{aligned} \tag{4}$$

The circuit, which realizes expressions (4) is shown in Figure 2, for $p = q = 1$, the time unit being the synaptic delay σ.

The circuit has the property of "reasoning" in the mode of "darii", but only the time intervals of the "conclusion" *"CiB"* are fixed; those of the major and minor premises being arbitrary within the limitation imposed on all such circuits, namely, that they are all integer multiples of σ.

From the standpoint of *formal* logic, we should have a circuit

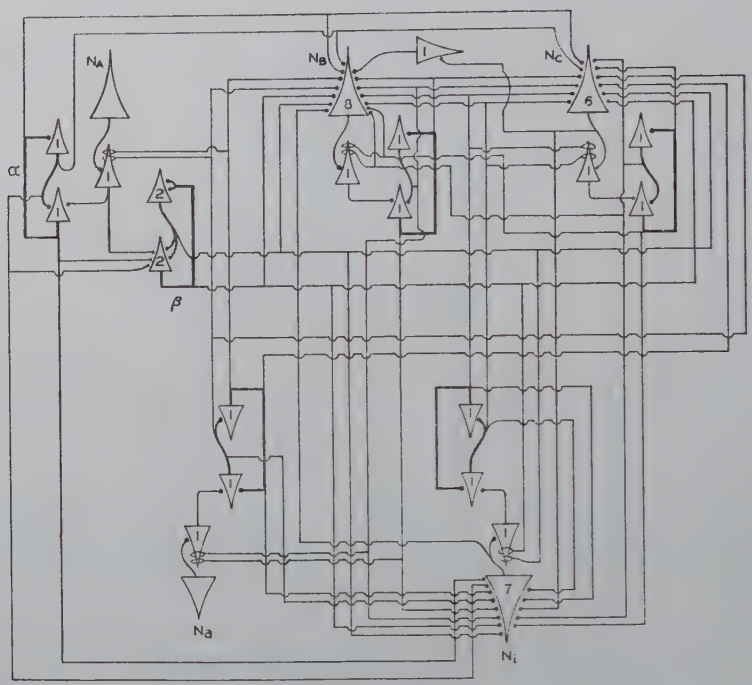

FIGURE 2

The threshold of the neurons are indicated by numbers. The reverberating circuit β becomes excited only when N_A fires for a second time. The first firing of N_A excites circuit α. The excitatory fibers from the two "halves" of circuit α provide the lower neuron of β with *one* impulse every σ. If then N_A is excited the second time, two simultaneous impulses are received by the lower neuron of β.

which not only gives $AaBCiA \rightarrow CiB$, but also $BaCAiB \rightarrow AiC$, as well as any other of the 6 permutations of ABC. To this end, we should connect in Figure 2 neuron N_B with N_A, N_a, N_i, N_B and N_C in the same manner as N_A is connected with N_B, N_a, N_i, N_B and N_C, etc. For the three stimuli alone we shall obtain a circuit of some sixty-nine neurons. (Some neurons may perhaps be used in common for all three circuits.) Approximately the same number of neurons will be required for the other eighteen modes. If we have M stimuli, which can be formally connected by a, e, i, o, then *any three* of those stimuli must be connected to N_a, N_e, N_i, and N_o so as to give any of the nineteen Aristotelian modes. Altogether this will require approximately

$$N = 69 \times 19 \frac{M!}{(M-3)!3!} \qquad (5)$$

neurons. For all practical purposes, M is infinite. Taking $M = 10^3$, which is too low an estimate, gives $N \sim 10^{11}$ neurons, which is biologically absurd, since the total number of neurons in the human brain is of the order of 10^{10}.

II

The solution of the difficulty may be sought in the following. When in formal logic we think (or say) "All *A*'s are *B*'s", the "*A*" stands actually for "the thing about which it is said "All . . . are". Similarly, "*B*" is merely the thing that follows "All *A*'s are". Hence in the circuit shown in Figure 2, for the mode "darii", N_A must be excited every time when *any other* stimulus precedes N_a; while N_B must be excited every time when *any other* stimulus follows N_a. Similar situations should hold for other circuits which correspond to other modes of logic. Hence we must construct a circuit such that if *any* neuron S_i fires before N_a, making a sequence S_iN_a, then S_i must become connected to N_A, so that henceforth *every* firing of S_i will be followed by a firing of N_A. The principle on which such a circuit is based is to have between each S_i and N_A a circle $C(S_i, N_A)$, Figure 3), the excitation of which is necessary for a permanent connec-

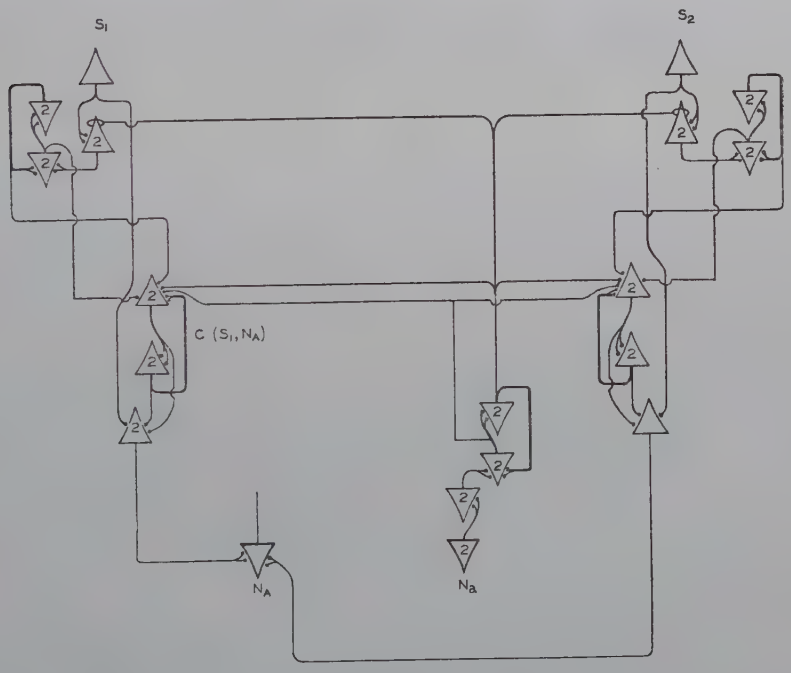

FIGURE 3

tion between S_i and N_A. If in expression (2) we substitute $C(S_iN_A)$ for N_3; S_i for N_1 and N_A for N_2, we obtain the expression describing the circuit. Such a circuit is shown on Figure 3 with only two S_i's. Any number of S_i's, however, can be used. The number of internuncials involved per S_i is only 6, so that if the total number of S_i's is M, 6 M neurons are needed.

If in the circuit shown in Figure 3 the sequence $S_1S_2N_a$ is presented, then both S_1 and S_2 become connected to N_A. In this case, $S_1 + S_2$ is actually the stimulus preceding N_a.

Since similar connections must be made between any S_i and N_B and N_C respectively, the total number of necessary neurons increases to 18 M. Next, connection between S_i's and N_A, N_B, and N_C must be made for sequences S_iN_i; S_iN_e; S_iN_o which would raise N to 72 M.

All those circuits, however, will still not fulfill all the requirements. The main difficulty arises when we have, for instance, a sequence $S_rAS_pS_pAS_q$, giving as a conclusion S_qiS_r (mode bamalip). Here S_p first follows "a" and then precedes it. Hence, after becoming connected to N_B, it will then become connected to N_A and confusion will result. Moreover, while in the above sequence S_r will be excited before N_a, due to time lags in the circuit of Figure 3 N_A may actually become excited *after* N_a, whereas for the working of the mechanism discussed in section I and exemplified in Figure 2 the excitation of N_A must precede that of N_a.

III

A way out of the difficulty may be found by taking a slightly different viewpoint. We may require that in any sequence, say $S_kAS_lS_miS_k$, constituting the premises of a syllogism, the *first* of the stimuli S connects with N_A, the *second*, different from the first with N_B and the *third* with N_C. Thus we will have the connection $S_k - N_A$; $S_l - N_B$; $S_m - N_C$.

In a sequence $S_rAS_pS_pAS_q$, S_r will become connected with N_A, S_p, with N_B and S_q with N_C. Since when a sequence, say $S_rAS_pS_pAS_q$ occurs, the sequence S_qiS_r must follow automatically, the connection between the S's and the corresponding N_A, N_B, or N_C must be two-way connections, so that excitation of N_A results in an excitation of S_r, etc. However, this two-way connection must not be a closed self-reverberating circuit, which will keep both S_r and N_A, or other corresponding pairs, excited indefinitely.

First we shall preoccupy ourselves with the problem of the connections *from* the S's to N_A, N_B, and N_C. Consider the structure represented in Figure 4. Let application of stimulus S_k result in the ex-

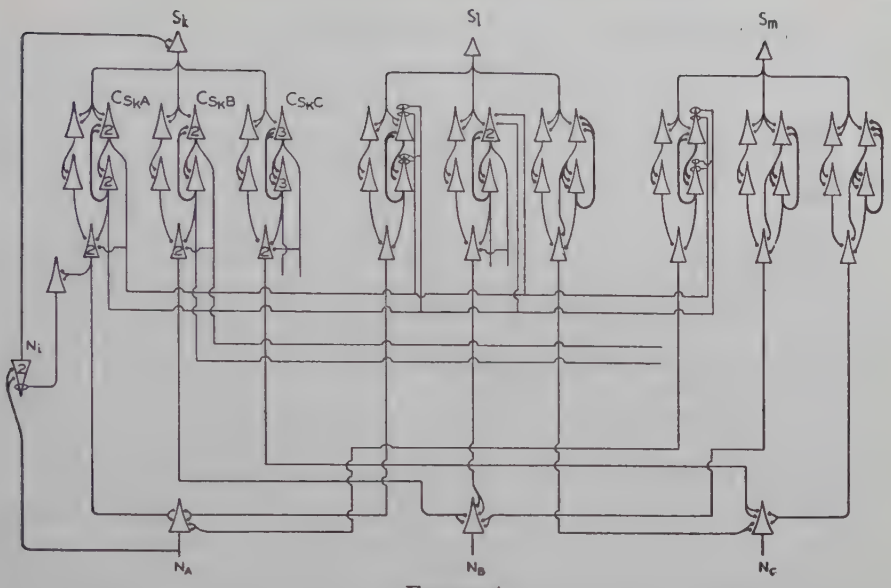

FIGURE 4

In order not to make the drawing too complicated, only a few connections are shown. Thresholds are indicated by numbers. The neurons of the circuit C_{S_kC} have a threshold 3, because they are excited only if besides S_k two other circuits C_{S_jA} and C_{S_lB} have already been excited. Those two circuits send each excitatory fiber to C_{S_kC}.

citation of neuron N_{S_k}, application of S_l in the excitation of N_{S_l}, and so forth. A simple firing of any S_k results in the permanent excitation of the circuits $C_{S_k}A$. Whenever a circuit of that kind is excited, a connection between S_k and N_A is established, and if we have $S_k(t)$, then, with the structure shown on Figure 4, we shall have $N_A(t+4)$.

If we denote by the symbol $S_{kA}(t)$ the statement that there exists at the time t a connection between S_k and N_A such that an excitation of S_k results in an excitation of N_A; if we denote by $C_{S_kA}(t)$ the statement that at the time t the circuit C_{S_kA} is excited, and by $S_j(t)$ the statement that S_j is excited at the moment t, then we have

$$S_{kA}(t) \equiv C_{S_kA}(t)\,;\, S_{kB}(t) \equiv C_{S_kB}(t)\,, S_{kC}(t) \equiv C_{S_kC}(t)\,. \qquad (6)$$

The requirements for our mechanism, mentioned in the first paragraph of this section, may now be written:

$$S_{kA}(t) \equiv (Ex)S_k(t-x) \cdot (\overline{Ej})S_{jA}(t) \cdot (j \neq k)\,; \qquad (7)$$

$$S_{lB}(t) \equiv (Ex)S_l(t-x) \cdot (Ei)S_{iA}(t) \cdot (\overline{Ej})S_{jB}(t) \cdot (i \neq l) \cdot (j \neq l); \tag{8}$$

$$S_{mC}(t) \equiv (Ex)S_m(t-x) \cdot (Ei)S_{iA}(t) \cdot (Ej)\, S_{jB}(t) \cdot (\overline{Er})S_{rC}(t) \cdot (i \neq m) \cdot (j \neq m) \cdot (r \neq m). \tag{9}$$

Introducing expressions (6) into (7), (8), and (9), we find

$$C_{S_kA}(t) \equiv (Ex)S_k(t-x) \cdot (\overline{Ej})C_{S_jA}(t) \cdot (j \neq k); \tag{10}$$

$$C_{S_lB}(t) \equiv (Ex)S_l(t-x) \cdot (Ei)C_{S_iA}(t) \cdot (\overline{Ej})C_{S_jB}(t) \cdot (i \neq l) \cdot (j \neq l); \tag{11}$$

$$C_{S_mC}(t) \equiv (Ex)S_m(t-x) \cdot (Ei)C_{S_iA}(t) \cdot (Ej)C_{S_jB}(t) \cdot (\overline{Er})C_{S_rC}(t) \cdot (i \neq m) \cdot (j \neq m); \quad (r \neq m). \tag{12}$$

In realizing expressions (10), (11), and (12) by a network, we see that the second term in the conjunction of the right side of expression (10) requires that each circuit C_{S_jA} send inhibitory fibers to all other circuits C_{S_pA}, where $p \neq j$. The second term of the conjunction on the right side of expression (11) indicates that every circuit C_{S_iB} must be thrown into excitation only if it is excited simultaneously by S_l and by the already excited circuit C_{S_kA}. According to expression (10) there can be only one such circuit at a time. Hence every circuit C_{S_kA} must send excitatory fibers to all circuits C_{S_jB} with $j \gtrless k$. The third term of the right side of expression (11) requires that each circuit C_{S_jB} would send inhibitory fibers to all other circuits C_{S_iB}, with $l \neq j$. A similar analysis of expression (12) shows that each circuit C_{S_iA} and C_{S_jB} sends excitatory fibers to each circuit C_{S_mC}, while each C_{S_rC} sends inhibitory fibers to all others C_{S_mC}, where $m \neq r$.

With this arrangement, which for sake of clarity is only partly shown in Figure 4, any of the neurons S_i which is excited first, will become connected to N_A; any S_i which is excited second, will become connected to N_B; and any S_i excited third will become connected to N_C.

It may be worth mentioning that such a mechanism provides us in principle with the theory of the concept of ordinal numbers. Instead of three neurons N_A, N_B, N_C, we may have a large number

N_1, N_2, $N_3 \cdots$, and every first stimulated S_i will connect to N_1, the second to N_2, etc. Thus, regardless of their nature the stimuli S become labelled: the first, the second, etc. Together with the mechanism for "counting" the number of repetitions of the same stimulus discussed before (Rashevsky, 1945b), we may have here a basis for a general theory of the conception of numbers.

There remains now to connect N_A (or N_B, or N_C) with the corresponding S_i, in such a way as to fulfill the requirements given at the beginning of this section. The way to do it is shown in Figure 4 for the connection between S_k and N_A. When S_k fires for the first time at the moment t, N_A will fire at $t+4$; but this firing will not make S_k fire again, because at $t+4$ the internuncial N_i receives also an inhibitory impulse. But if at any time after the connection S_{kA} is established, N_A fires, then S_k will fire two σ's later.

Hence when, for instance, a sequence $S_k a S_l S_m i S_k$ produces the sequence $N_A a N_B N_C i N_A$, which, by means of the mechanism shown in Figure 2, produces $N_C i N_B$, the sequence $S_m i S_l$ will result, provided the time lag between the firing of N_C and of N_i is greater than that between N_C and S_k. This can always be achieved by making in expressions (4) p and q sufficiently large. In fact, it is sufficient to have $p > 2$. This can be obtained by adding an appropriate amount of internuncials in the circuit of Figure 2.

Finally, a mechanism must be added which disconnects the S_i's from N_A, N_B, and N_C, as soon as the syllogism is completed. This can be done by having a neuron N_F respond to, and only to, the whole sequence, say $N_A a N_B N_C i N_A N_C i N_B$, which can be obtained by realizing expressions similar to expression (4). Then make N_F send inhibitory fibers to *all* circuits $C_{S_i A}$, $C_{S_i B}$, $C_{S_i C}$.

With the mechanism discussed in this section and represented in Figure 4, there are 17 interneurons corresponding to each S_i. Hence the total number of neurons necessary is 17 M. Even with M 10^5, which is the order of magnitude of the sensory fibers reaching the sensory projection areas of the cortex, we find the total number to be about 2×10^6, which is a very small portion of all neurons available. The total number of neurons involved in mechanisms like that shown in Figure 2 will including all additional internuncials, discussed above, not exceed the same figure, so that all told $N \sim 2 \times 10^6$ neurons.

IV

All the above discussions are of interest as providing a mechanism for logical thinking. The theory is, however, not directly amenable to quantitative predictions and experimental tests. To obtain that, we must consider possible failures of the mechanism, and at-

tempt to evaluate the probabilities of correct and wrong conclusions or of the inability of making a conclusion at all (Rashevsky, 1945a). One of the ways of developing a theory of errors in the present case is to consider that the neurons N_a, N_i, N_e, and N_o are excited by a previous excitation of four corresponding pathways, *I*, *II*, *III*, and *IV*, which are activated by stimuli S_a, S_i, S_e, and S_o, which are cross-inhibiting each other, as discussed previously (Rashevsky, 1938). We have here a generalization to four stimuli of H. D. Landahl's (1938) circuit. Now N_a will fire only if S_a is much stronger than the other stimuli, and so on. But due to fluctuations of excitation in a certain percentage of cases, N_i may, for example, become excited, although S_a is applied. General expressions for the probabilities of such occurrences have been given by H. D. Landahl (1938). They may be elaborated and applied to our problem. An error in logical thinking is ascribed according to this picture of the fact, that although for instance, actually $S_kS_aS_l$ is presented, the central mechanism will give $S_kN_iS_e$. A confusion thus results.

If we have a chain of syllogisms, as discussed before (Rashevsky, 1945a), we must keep in mind that in the present theory each syllogism of the chain is the result of functioning of the *same* mechanism which every time simply becomes connected to different stimuli S_i. Hence we cannot talk of mutual inhibition or excitation of the different units. Instead we may consider fatigue phenomena, which raise the thresholds of the tracts *I*, *II*, *III*, and *IV*, with repeated use; or we may consider facilitation phenomena, which decrease those thresholds with repetition. Since the probabilities of the correct or wrong conclusions are functions of those thresholds, we shall thus again obtain expressions for the probability of a correct or wrong conclusion of a whole set of syllogisms in terms of the total number of syllogisms required by the problem.

The difficulty mentioned in the previous paper (Rashevsky, 1945b) remains; namely, the necessity of having all intervals between the stimuli $S_kS_lS_m$, etc. be exactly integer multiples of σ. This difficulty may be overcome, as suggested in *loc. cit.*, by constructing corresponding "macro-circuits". In the present instance, however, we may run into the difficulty of requiring more neurons than are actually available.

A different solution of the difficulty leads to interesting consequences and suggestions. If the intervals between the stimulation of N_A, N_a, N_B, N_i, and N_C are all integer multiples of σ, then, for instance, all eight terminal bulbs synapsing with neuron N_B in Figure 2 will be receiving simultaneously impulses at regular intervals σ. If, however, the above mentioned intervals between the excitation of the

neurons N_A, N_a, etc. are not integer multiples of σ, then while each bulb will receive impulses at regular intervals σ, they will not act synchronously, and neuron N_B will not fire at all, if the impulses do not fall within the period of latent addition. This, however, would be the case only if all synaptic delays were perfectly constant and all equal to σ. Such a situation appears to be biologically rather unplausible. It is more likely that while the synaptic delay of a given neuron is *on the average* equal to σ, it actually fluctuates around that value according to some distribution function. Let τ be the actual synaptic delay, then the probability of a given value of τ, $\tau + d\tau$ will be given by

$$F(\tau)\,d\tau, \tag{13}$$

with

$$\int_0^\infty F(\tau)\,d\tau = 1; \qquad \int_0^\infty \tau F(\tau)\,d\tau = \sigma. \tag{14}$$

Instead of being concentrated all at the ends of the interval σ, the eight impulses arriving at N_B now are distributed at random within the interval σ. If τ were constant, then the distribution of the individual impulses within the interval σ would be the same for all consecutive intervals. But because of the fluctuations of τ, this distribution will vary from interval to interval σ. We may ask for the probability that, due to fluctuations, all eight impulses fall within the period σ_l of latent addition. The greater the dispersion of $F(\tau)$, the greater will be this probability, and therefore the shorter the probable time which it will take for this event to occur. But this probable time measures the probable speed of response to the premises of the syllogism, or speed of reasoning. For zero dispersion of $F(\tau)$, that is, for a constant τ $(= \sigma)$, the probability will be zero and the speed of reasoning zero.

The actual calculation of the probability would have to proceed as follows: for a given average distribution of impulses in the interval σ we can calculate the probability of each impulse to fall within a given fixed interval σ_l, and take the product of all those probabilities. Then we shall have to sum over all possible positions of σ_l within σ. Finally we shall have to sum over all possible average distributions of the impulses, which are determined by the exact intervals (N_A, N_a); (N_a, N_B); (N_C, N_i), (N_i, N_A). Here we would have to consider the finite duration τ^* of an impulse, and consider the probability of a given position of any impulse in the interval σ as equal to τ^*/σ. The probability of a given distribution is then $(\tau^*/\sigma)^n$, where n is the number of impulses considered. (In the present instance, $n = 8$.) The total number of possible distributions would be equal to the num-

ber of possible ways of selecting n numbers out of $(\sigma/\tau^*) > n$. This is

$$\frac{(\sigma/\tau^*)\,!}{[(\sigma/\tau^*) - n]\,!\,n!}. \tag{15}$$

The details of such calculations will be discussed in a separate paper. We shall end, however, by making the following important remark. The same considerations apply to the mechanism for counting, discussed before (Rashevsky, 1945b); they will lead to an expression for the maximum speed with which a stimulus may be repeated and still be able to be counted. Assuming that the function $F(\tau)$ is the same for the whole cortex, we shall find a relation between speed of logical reasoning, and this limiting speed in counting. Both will vary from individual to individual.

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